Dykema Docket No. 065379-0053

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

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| Joerg ROSENBERG *et al.* | | Examiner: | Jennifer Y. CHO |
| Serial No.: | 10/539,505 | Group Art Unit No.: | 1621 |
| Filing Date: | December 16, 2003 | Confirmation No. : | 4705 |

For:

FORMULATION COMPRISING FENOFIBRIC ACID, A PHYSIOLOGICALLY ACCEPTABLE SALT OR DERIVATIVE THEREOF

**AMENDMENT**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

In response to the Office Action mailed on September 17, 2007, Applicants respectfully request reconsideration in light of the following amendments and remarks. This Amendment is also being submitted with a Request for Continued Examination (RCE). Applicants also Petition herewith for a Five Month Extension of Time, thus extending the due date for response from May 11, 2008 until October 11, 2008. The Commissioner is authorized to charge the fee associate with the RCE, the Extension of Time fee and any other fees that may be due or owing in connection with this application to deposit account number 04-2223.

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LISTING OF THE CLAIMS

1. (Cancelled).

2. (Cancelled).

3. (Cancelled).

4. (Cancelled).

5. (Cancelled).

6. (Cancelled).

7. (Cancelled).

8. (Cancelled).

9. (Cancelled).

10. (Cancelled).

11. (Cancelled).

12. (Cancelled).

13. (Cancelled).

14. (Cancelled).

15. (Cancelled).

16. (Cancelled).

17. (Cancelled).

18. (Cancelled).

19. (Cancelled).

20. (Cancelled).

21. (Cancelled).

22. (Cancelled).

23. (Previously Presented). A pharmaceutical composition comprising:
fenofibric acid or a salt thereof; and
at least one binder.

24. (Previously Presented). The pharmaceutical composition of claim 23, wherein the composition further comprises a coating.

25. (Previously Presented). The pharmaceutical composition of claim 23, wherein the binder is an enteric binder.

26. (Previously Presented). The pharmaceutical composition of claim 25, wherein the enteric binder is an enteric polymer.

27. (Previously Presented). The pharmaceutical composition of claim 26, wherein the enteric polymer is selected from the group consisting of hydroxypropylmethylcellulose phthalate, hydroxypropylmethylcellulose acetate succinate, carboxymethylethylcellulose, cellulose acetate phthalate, cellulose acetate trimellitate and carboxymethylcellulose sodium.

28. (Previously Presented). The pharmaceutical composition of claim 27, wherein the enteric polymer is selected from copolymers based on (meth)acrylic acid and at least one alkyl (meth)acrylic acid ester.

29. (Previously Presented). The pharmaceutical composition of claim 28, wherein the alkyl (meth)acrylic acid ester is methyl methacrylate.

30. (Previously Presented). The pharmaceutical composition of claim 29, wherein the copolymers have a ratio of free carboxyl groups to esterified carboxyl groups of 2:1 to 1:3.

31. (Previously Presented). The pharmaceutical composition of claim 30, wherein the ratio is 1:1.

32. (Previously Presented). The pharmaceutical composition of claim 23, wherein the fenofibric acid or salt thereof comprises 5 to 60% by weight of the composition.

33. (Previously Presented). The pharmaceutical composition of claim 23, wherein the binder is a non-enteric binder.

34. (Previously Presented). The pharmaceutical composition of claim 33, wherein the non-enteric binder is selected from the group consisting of: a synthetic polymer, a modified natural polymer, a natural polymer and a nonpolymeric binder.

35. (Previously Presented). The pharmaceutical composition of claim 23, wherein the composition is a tablet.

36. (Previously Presented). The pharmaceutical composition of claim 23, wherein the composition is a capsule.

37. (Previously Presented). A method for oral administration of fenofibric acid or salt thereof, comprising administering the pharmaceutical composition of claim 23.

## REMARKS

*Interview Summary*

The undersigned attorney would like to thank Examiners Cho and Eyler for the courtesies extended during the in person interview conducted on March 31, 2008 involving the undersigned attorney, Ms. Johanna Corbin, Ms. Irene Reininger and Dr. Guenter Blaich. During the interview, the prior art rejections of record were discussed. Discussed first was the rejection of claim 23 under 35 U.S.C. Section 102(b) as being anticipated by Boyer (U.S. Patent No. 4,800,079). In response to this rejection, the undersigned attorney pointed out to the Examiners that Boyer teaches **only** fenofibrate, not fenofibric acid. The Examiners agreed and stated that the 35 U.S.C. Section 102(b) rejection in view of Boyer would be withdrawn.

With respect to the rejection of claims 23-37 under 35 U.S.C. Section 103(a) as being unpatentable over Boyer in view of Kothrade (U.S. Patent No. 6,284,803), the undersigned attorney and Dr. Blaich argued that the article by Gurrieri, J. et al., *Drug Res.,* 26(5) (1976) taught one skilled in the art away from using fenofibric acid due to gastrointestinal toxicity. Against this prevailing view, later experiments conducted in-house showed no gastrointestinal toxicity for fenofibric acid. The undersigned attorney indicated that this information would be made of record in a 37 C.F.R. Section 1.132 declaration.

*Rejection of Claims under 35 U.S.C. Section 102(b)*

The Office has rejected claim 23 under 35 U.S.C. Section 102(b) for being anticipated by Boyer (U.S. Patent No. 4,800,079). Specifically, the Examiner says that Boyer teaches a pharmaceutical composition comprising fenofibrate and a binder. Applicants respectfully traverse the rejection.

As discussed during the interview with Examiners Cho and Eyler on March 31, 2008, Boyer does not teach fenofibric acid as currently recited in the claims. Therefore, because Boyer fails to teach each and every element of the claimed invention, and as agreed to by the Examiners during the interview, this rejection should be withdrawn.

*Rejection of Claims Under 35 U.S.C. Section 103(a)*

Claims 23-37 are rejected under 35 U.S.C. Section 103(a) as being unpatentable over Boyer in view of Kothrade et al. (U.S. Patent No. 6,284,803). The Examiner says that Boyer teaches a pharmaceutical composition of fenofibrate and a binder but is deficient in that the limitations of the dependent claims are "not explicitly stated in the composition." The Examiner cites Kothrade et al. as reciting the limitations of

the dependent claims. Specifically, the Examiner says that it would be *prima facie* obvious to one of ordinary skill in the art at the time of the invention to combine the components of Kothrade et al. for the formulation of Boyer to arrive at a fenofibrate composition for pharmaceutical oral administration. According to the Examiner, the "expected" result would be an effective lipid-regulating tablet in dosage form. Applicants respectfully traverse.

As discussed above, Boyer teaches fenofibrate and does not disclose or suggest fenofibric acid. Kothrade et al. is directed to solid dosage forms that comprise a polymeric binder and an active ingredient, wherein the polymeric binder consists of copolymerized units of (1) 15-83% w/w of at least one N-vinyllactam; (2) 15-83% w/w of methyl methacrylate; (3) 2-70% of at least one other monomer; and (4) 9-9.9% w/w of at least one α,β-ethylenically unsaturated acid. Kothrade et al. teach in detail how to make the polymeric binder. Kothrade et al. do not disclose or suggest fenofibric acid. Thus, neither Boyer nor Kothrade et al., either individually or collectively, disclose or suggest formulating fenofibric acid into a composition.

As discussed during the March 31, 2008 interview, Applicants submit that there is a good reason why neither Boyer and Kothrade et al., either individually or collectively, disclose or suggest formulating fenofibric acid into a composition. Applicants believe that the reason is that the prior art taught away from formulating fenofibric acid into a composition due to its side effects, namely, gastrointestinal toxicity. Specifically, enclosed herewith, in Exhibit B, is an article by Gurrieri, J. et al., *Drug Res.,* 26(5) (1976) ("Gurrieri"). Generally, Gurrieri describes the hypolipidemic drug, isopropyl-[4'-(p-chlorobenzoyl)-2-phenoxyl]-propionate (LF178 (fenofibrate)) and studies involving this drug and its major circulating metabolite, phenoxy-isobutryic acid, in rats. LF178 and the sodium salt of phenoxy-isobutryic acid (LF 153 (fenofibric acid)) were administered to rats in doses ranging from 50-300 mg/kg. LF 153 was found to exhibit significant side effects at doses exceeding 200 mg/kg (See, Figure 2 ). Gurrieri states on page 893 underneath Table 9 that "the acid metabolite LF 153 did induce significant lesions at 300 mg/kg."

As discussed in the attached 37 C.F.R. Section 1.132 Declaration of Guenter Blaich ("Blaich Declaration"), once Gurrieri was published, no one skilled in the art appeared to dispute the results of this article (See, Blaich Declaration, Paragraph 3). Because no one skilled in the art disputed these results, Applicants submit that Gurrieri actually teaches one skilled in the art away from formulating fenofibric acid into a composition because of gastrointestinal toxicity. Therefore, Applicants also submit that since the publication of Gurrieri, those skilled in the art were actually discouraged from developing compositions containing fenofibric acid because of this side effect. Rather, instead of focusing on fenofibric acid, Applicants submit that those skilled in the art focused on finding other ways of formulating fenofibrate,

despite the fact that fenofibrate is known to be poorly soluble[1] and difficult to formulate. This is exemplified in that since 1976, at least three different approaches were developed by those skilled in the art to improve the bioavailability of **fenofibrate**. These approaches are: (1) reducing the size of fenofibrate (to increase the surface area thus resulting in better dissolution); (2) creating solid dispersions of fenofibrate (the amorphous form should exhibit faster dissolution); and (3) using lipid systems (used to solubilize fenofibrate).

In December 1997, Abbott Laboratories[2] and Fournier Pharma ("Fournier") signed an agreement to develop, register, market, use and sell fenofibrate and metabolites thereof, including fenofibric acid. During a Fournier fenofibric acid development meeting in April 2001, the Gurrieri article was discussed (See Blaich Declaration, Paragraph 5). According to notes made during this meeting, it was determined that the dose of fenofibric acid administered in Gurrieri far exceeded the amount normally used to reduce lipids in rats and that further safety and pharmacology studies would be needed to identify safe dosages of fenofibric acid in rats (See Blaich Declaration, Paragraph 5).

In August and October 2001, at least three (3) toxicology and pharmacokinetic studies were performed by Fournier using micronized fenofibrate, fenofibric acid and salts of fenofibric acid (See, Blaich Declaration, Paragraph 6). In one study, the gastric ulcerogenic effect and pharmacokinetics of micronized fenofibrate (FEN) and fenofibric acid (FA) were evaluated. Specifically, male and female rats were orally administered a single dose of 100 mg/kg, 300 mg/kg or 1000 mg/kg of micronized fenofibrate or fenofibric acid. The rats were placed on a water-only fast the day prior to the study. The pharmacokinetic data from the study is shown in Table A.

**Table A**

| Test compound | Dose (mg/kg) | Cmax (μg/mL) Males/Females | AUC (μg•h/mL) Males/Females |
|---|---|---|---|
| FEN | 100 | 85.7/243 | 1757/5752 |
| | 300 | 195/391 | 4875/10132 |
| | 1000 | 310/417 | 7528/12382 |
| FA | 100 | 396/454 | 5414/11135 |
| | 300 | 579/688 | 12382/22353 |
| | 1000 | 903/1075 | 29223/42646 |

Administration of 1000 mg/kg of fenofibric acid to the rats was found to be lethal. With respect to toxicology, statistically significant ulcerogenic activity were found in rats administered 1000 mg/kg of fenofibric

[1] In contrast to fenofibrate, which is highly insoluble, fenofibric acid is highly soluble.
[2] Abbott Laboratories ("Abbott") is the parent company of Abbott GmbH & Co. KG, the assignee of the present invention.

acid. The damage was located in the corpus of the stomach. At the lower doses of 100 and 300 mg/kg, no statistically significant ulcerogenic activity was observed.

In the second study, the gastric ulcerogenic effect and pharmacokinetics of fenofibric acid ("FA"), the lysine salt of fenofibric acid ("FA-Lysine") and the arginine salt of fenofibric acid ("FA-Arginine") were evaluated. Specifically, male and female rats were orally administered a single dose of 300 mg/kg or 1000 mg/kg of fenofibric acid, the lysine salt of fenofibric acid or the arginine salt of fenofibric acid following a 4-day observation period. The pharmacokinetic data from the study is shown below in Table B.

Table B

| Test compound | Dose (mg/kg) | Cmax (µg/mL) Males/Females | AUC (µg•h/mL) Males/Females |
|---|---|---|---|
| FA (Reference) | 1000 | 767/951 | 23896/46314 |
| FA-Lysine | 300 | 517/761 | 12327/26652 |
| | 1000 | 869/1262 | 25957/11351# |
| FA-Arginine | 300 | 487/695 | 10601/23382 |
| | 1000 | 865/1198 | 16032/11544# |

# - Lethal dose with limited PK

Administration of 1000 mg/kg of fenofibric acid and the lysine and arginine salts of fenofibric acid to the rats was found to be lethal. With respect to toxicology, statistically significant ulcerogenic effects were found in rats administered 300 mg/kg and 1000 mg/kg of the lysine and arginine salts of fenofibric acid. Statistically significant gastric ulcerations were also found in rats administered 1000 mg/kg of fenofibric acid.

In the third study, a two week gavage study was performed with female rats. In this study, a tube was inserted into the mouth of the rats who were orally administered 100 mg/kg, 300 mg/kg or 500 mg/kg of micronized fenofibrate or fenofibric acid for 14 consecutive days. The pharmacokinetic data from the study is shown below in Table C.

Table C

| Test compound | Dose (mg/kg/day) | Cmax (µg/mL) | AUC (µg•h/mL) |
|---|---|---|---|
| FEN | 100 | NA | 5442 |
| | 300 | NA | 10632 |
| | 500 | NA | 13915 |
| FA | 100 | NA | 9386 |
| | 300 | NA | 14312 |
| | 500 | NA | 16678 |

NA: Not available.

Statistically significant gastric ulcerations were found in rats administered 300 mg/kg and 500 mg/kg of fenofibric acid.

During another Fournier fenofibric acid development meeting in December 2001, the above three studies were discussed (See, Blaich Declaration, Paragraph 7). According to notes made during this meeting, a comment was made that these studies showed the potential of ulcerogenicity with fenofibric acid at higher doses (1000 mg/kg) and it was surmised that this could be the result of both to a local effect, but also to a higher systemic exposition (See Blaich Declaration, Paragraph 7).

A further Fournier fenofibric acid development meeting was held in January 2002 (See, Blaich Declaration, Paragraph 8). According to notes made during this meeting, a comment was made that a formal dose ranging study was going to be required to understand the gastrointestinal side effects associated with fenofibric acid (See, Blaich Declaration, Paragraph 8). According to Dr. Blaich's understanding, at the time of this meeting, it was believed that there was a problem with fenofibric acid in terms of its side effects and that formulation work was necessary (See, Blaich Declaration, Paragraph 8).

In January 2002, Abbott retained Hugh E. Black & Associates, Inc. ("Hugh Black") to review the data that Fournier had generated regarding fenofibric acid to advise as to a possible developmental pathway for fenofibric acid (See, Blaich Declaration, Paragraph 9). In September 2002, a meeting was held at Abbott to review the recommendations of Hugh Black (See, Blaich Declaration, Paragraph 10). Hugh Black recommended that Abbott conduct a 90 day toxicity study with fenofibric acid ((See, Blaich Declaration, Paragraph 10).

In approximately June or July 2003, Dr. Blaich became responsible for Abbott's fenofibric acid development program (See, Blaich Declaration, Paragraph 11). At that time, it was Dr. Blaich's understanding that the gastrointestinal side effects associated with fenofibric acid were still an issue and that Abbott needed to conduct studies to examine and understand the nature of these side effects (See, Blaich Declaration, Paragraph 11).

Thus, from November 2003 through March 2005, five (5) studies were performed by Abbott to examine the gastrointestinal side effects associated with fenofibric acid and salts of fenofibric acid (See, Blaich Declaration, Paragraph 11). In these studies, the gastric ulcerogenic effect and pharmacokinetics of micronized fenofibrate ("FEN"), fenofibric acid ("FA") and the calcium and choline salts of fenofibric acid were evaluated. The first study was a 5-week palatability study. In this study, the rats were administered Rodent Chow, 100 mg/kg/day or 300 mg/kg/day of micronized fenofibrate. The second study was a 5-week palatability study. In this study, the rats were administered Rodent Chow, 10 mg/kg/day, 30 mg/kg/day, 75 mg/kg/day or 150 mg/kg/day of fenofibric acid. The third study was a 2-week gavage study. In this study, the rats were administered Rodent Chow, 30 mg/kg/day, 100 mg/kg/day or 300 mg/kg/day of

the calcium salt of fenofibric acid ("FA-Calcium"). The fourth study was a 2-week gavage study. In this study, the rats were administered Rodent Chow, 30 mg/kg/day, 100 mg/kg/day or 300 mg/kg/day of the choline salt of fenofibric acid ("FA-Choline"). The fifth study was a 3-month gavage study. In this study, the rats were administered Rodent Chow, 10 mg/kg/day, 30 mg/kg/day or 100 mg/kg/day of the FA-Choline. The pharmacokinetic data for the highest doses of fibrofibrate, fenofibric acid or the calcium and choline salts of fenofibric acid is provided below in Table D.

Table D

| Test compound | Study Type | Dose (mg/kg/day) | Cmax (µg/mL) Males/Females | AUC (µg•h/mL) Males/Females |
|---|---|---|---|---|
| FEN | 5-week palatability | 300 | 677/842 | 15274/19333 |
| FA | 5-week palatability | 150 | 611/787 | 14423/20237 |
| FA-Calcium | 2-week gavage | 300 | 682/650 | 14171/13452 |
| FA-Choline | 2-week gavage | 300 | 702/747 | 12148/15305 |
| FA-Choline | 3-Month gavage | 100 | 609/679 | 12021/12194 |

In each of the above studies, no gastric ulcerations were detected at any dose.

According to Dr. Blaich, the first and second studies conducted by Abbott were designed to match the exposure levels (namely AUC) seen in the two week gavage study performed by Fournier the results of which are shown above in Table C (See, Blaich Declaration, Paragraph 12). In these two studies, the exposure levels (AUC) exceeded the anticipated AUCs (based on the Fournier study) but nonetheless, the rats did not show any evidence of gastric ulcerations (See, Blaich Declaration, Paragraph 12). The 2-week gavage studies performed by Abbott using the calcium and choline salts of fenofibric acid produced plasma exposure levels between 12148 and 15305 µg•h/mL, but in none of these studies were any gastric ulcerations in the rats observed (See, Blaich Declaration, Paragraph 12). Finally, a 3 month rat study was conducted using lower dosages of the choline salt of fenofibric acid[3]. In this study, plasma exposure levels between 12021 and 12194 µg•h/mL resulted, but no gastric ulcerations in the rats were observed (See, Blaich Declaration, Paragraph 12). Thus, despite plasma exposure levels (AUC) up to 20237 µg•h/mL and Cmax levels up to 787 µg/mL, no gastric ulcerations were observed in the Abbott studies involving fenofibric acid or the calcium and choline salt of fenofibric acid (See, Blaich Declaration, Paragraph 12). According to Dr. Blaich, the reason for the different outcome between the Abbott studies and the studies conducted by Fournier is unknown but was very surprising (See, Blaich Declaration, Paragraph 12). After completion of these studies, Abbott and Fournier moved ahead with developing a fenofibric acid formulation.

A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant. *In re Gurley* 27 F.3d 551, 553 (Fed. Cir. June 1994). According to the Federal Circuit, "The degree of teaching away will of course depend on the particular facts; in general, a reference will teach away if it suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant." *Id.*

Applicants submit that after the publication of Gurrieri in 1976 that those skilled in the art were led in a different direction or different path than that of formulating fenofibric acid (which is a **highly soluble** drug) into a composition. As discussed previously herein, it is believed that after 1976, because of the side effects described in Gurrieri, those skilled in the art focused their efforts on developing different ways of formulating fenofibrate, a highly **insoluble drug**. As discussed in the Blaich Declaration, no one questioned the findings of Gurrieri. Approximately twenty-five plus years later, after several studies were conducted by the Abbott and Fournier, it was surprisingly discovered that fenofibric acid did not cause gastrointestinal side effects as previously believed, and that fenofibric acid could be formulated into a composition.

In view thereof, Applicants submit that the claimed invention is not obvious and that this rejection is now moot and should be withdrawn.

## REQUEST FOR RECONSIDERATION

Reconsideration and withdrawal of all claim rejections are respectfully requested. Applicants believe that the present application is in condition for allowance. Should the Examiner have any questions or would like to discuss any matters in connection with the present application, the Examiner is invited to contact the undersigned at

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October 7, 2008

[3] The lower dosages of the choline salt of fenofibric acid were used in this study because of other types of toxicity, namely, skeletal muscle and myofiber degeneration and decreased body weight gain.

Date: October 2008

Direct telephone calls to: 312.627.2184

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